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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,162	12/11/2001	Ted B. Usdin	NIH175.001C1	2740

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/014,162	USDIN ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *7 and 20-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 20-25* is/are rejected.

7)☒ Claim(s) *26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 08/08/2005 has been entered. Claims 7, 20-26 are pending and being examined.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 112

Claims 7 and 20-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues that the skilled artisan would conclude that Applicant was in possession of the necessary common attributes possessed by members of the genus. Referring to paragraph 7 of the declaration of Dr. Usdin, Applicant argues that structure-function relationships are found in prior art PTH2 receptor ligands and their close relatives PTH1 receptor ligands. Referring to paragraph 8 of the declaration of Dr. Usdin, Applicant argues that post-date references demonstrates that TIP39 tolerates considerable amino acid sequence variation. The declaration under 37 CFR 1.132 filed 08/08/2005 is insufficient to overcome the rejection of claims 7 and 20-25 based upon a lack of written description under 35 U.S.C. § 112, first paragraph, as set forth in the last Office action because: Declarant argues that because of the relationship of TIP39 to PTH and to PTHrP one could reasonably anticipate natural variation in TIP39 from different species, and further that artificially induced variation in many residues within the sequence would be tolerated with little effect on binding to the PTH2 receptor. Declarant argues

that Hansen (Exhibit 7) and Papasani (Exhibit 8) are post-filing date art confirming that TIP39 tolerates considerable amino acid sequence variation. Declarant's arguments have been fully considered but they are not persuasive.

Papasani (Exhibit 8) teaches that a comparison of zebrafish and human TIP39 amino acid sequences may provide insights in identifying critical regions for receptor binding and activation (page 5301, right column, last full paragraph).

Usdin (Trends Pharmacol Sci. 2000 Apr;21(4):128-30) teaches that:

> Activation of the human PTH_2 receptor by TIP39 and PTH, together with the lack of PTH_1 receptor activation by TIP39, could allow the functional characterization of additional residues by exchanges between these peptides, and comparison of the effects of the new peptide on the two receptor types. Equivalent effects at the human PTH_2 receptor, despite very limited sequence identity, suggest that: (1) TIP39 and PTH might have different binding sites; (2) the few identical residues are involved in contact; or (3) apparently different amino acids possess similar functions. It should be possible to tease these possibilities apart by studying appropriate peptide and receptor modifications. Page 129, paragraph bridging left and center columns.

Papasani (Exhibit 8) and Usdin (Trends Pharmacol Sci. 2000 Apr;21(4):128-30) are evidence that a the time of applicant's filing the critical regions for receptor binding and activation and the appropriate peptide modifications were not known. Papasani (Exhibit 8) and Usdin (Trends Pharmacol Sci. 2000 Apr;21(4):128-30) are sufficient evidence to indicate that skilled artisans could not predict the operability of other species other than the single one disclosed in the specification. Neither the specification, Papasani (Exhibit 8), nor Usdin (Trends Pharmacol Sci. 2000 Apr;21(4):128-30) teach the appropriate modifications. Furthermore, Papasani's zTIP39 was unknown at the time of filing. The only comparative data available at the time of filing were the bovine and human amino acid sequences, which the specification

indicates are identical. The only correlation between structure and function is 100% identity. This identity does not fairly represent the variation within the entire claimed genus.

Hansen (Exhibit 7) indicates that the overall amino acid sequence identity between TIP39, PTH, and PTHrP is very low (paragraph bridging pages 101-102). The N-terminal alpha helix of TIP39, which seems to be responsible for P2R activation, is identical in man and mouse, whereas the C-terminal alpha helix, which is important for receptor binding, differs in four aa positions, being apparently responsible for the different binding properties of murine and human TIP39 (page 102, left column, full paragraph 1). This identity does not fairly represent the variation within the entire claimed genus.

Furthermore, Usdin (Trends Pharmacol Sci. 2000 Apr;21(4):128-30) indicates that the TIP39 and the PTH_2 receptor constitute a relatively uncharacterized peptide–receptor system (page 128, first paragraph), which indicates that the TIP39 and PTH_2 receptor interaction is not well-characterized or well-developed. Furthermore, TIP39 appears to be distantly related to PTH and PTHrP (page 129, left column, full paragraph 2).

The written description does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. It extends only to that which is disclosed. One shows that one is in possession of the invention by describing the invention, with all its claimed limitations, not that which makes it obvious. The evidence does not convey with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was in possession of the claimed invention. The evidence does not clearly allow persons of ordinary skill in the art to recognize that Applicant invented what is claimed.

Claims 7 and 20-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a peptide comprising the amino acid sequence of SEQ ID NO: 1, does not reasonably provide enablement for polypeptide having the recited percent identity thereto wherein said polypeptide has PTH2 or PTH1 receptor binding activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant argues that the specification provides considerable guidance for making variants of SEQ ID NO: 1 and assays are provided that will identify those peptides having the required activity. Referring to paragraph 7 of the declaration, Applicant argues that the discovery of TIP39 in combination with the comparison to PTH and PTHrP demonstrate that considerable variation is was known to be tolerated. Referring to paragraph 8 of the declaration, Applicant argues that post-filing date art confirms that TIP39 tolerates considerable amino acid sequence variation. Applicant argues that because the skill level was high and all the methods needed to practice the invention were known, the experimentation required would not be undue. The declaration under 37 CFR 1.132 filed 08/08/2005 is insufficient to overcome the rejection of claims 7 and 20-25 based upon scope of enablement under 35 U.S.C. § 112, first paragraph, as set forth in the last Office action because: Declarant argues that because of the relationship of TIP39 to PTH and to PTHrP one could reasonably anticipate natural variation in TIP39 from different species, and further that artificially induced variation in many residues within the sequence would be tolerated with little effect on binding to the PTH2 receptor. Declarant argues that Hansen (Exhibit 7) and Papasani (Exhibit 8) are post-filing date art confirming that TIP39

tolerates considerable amino acid sequence variation. Declarant's arguments have been fully considered but they are not persuasive. The first paragraph of 35 U.S.C. 112 requires that the scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. The issue is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance provide by the present specification and the prior art of record.

Papasani (Exhibit 8) teaches that a comparison of zebrafish and human TIP39 amino acid sequences may provide insights in identifying critical regions for receptor binding and activation (page 5301, right column, last full paragraph).

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Furthermore, Usdin (Trends Pharmacol Sci. 2000 Apr;21(4):128-30) indicates that the TIP39 and the PTH_2 receptor constitute a relatively uncharacterized peptide–receptor system (page 128, first paragraph), which indicates that the TIP39 and PTH_2 receptor interaction is not

well-characterized or well-developed. Furthermore, TIP39 appears to be distantly related to PTH and PTHrP (page 129, left column, full paragraph 2).

The present claims are not limited to naturally occurring compounds and the present specification does not provide a repeatable, predictable process of producing a peptide with PTH1 or PTH2 receptor binding activity, whose amino acid sequence deviates from the single disclosed, naturally occurring sequence by as much as 70%. To practice the present invention in a manner consistent with the breadth of the claims would not require just a repetition of work that is described in the present application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues in the amino acid sequence of SEQ ID NO: 1 which are required for the functional and structural integrity of that protein. It is this additional characterization of that single disclosed, naturally occurring protein that is required in order to obtain the functional and structural data needed to permit one to produce a protein which meets both the structural and functional requirements of the present claims that constitutes undue experimentation.

The first paragraph of 35 U.S.C. § 112 requires that the breadth of the claims must be based upon the predictability of the claimed subject matter and not on some standard of trial and error. To argue that one can make material embodiments of the invention and then test for those that work in the manner disclosed or that the present claims only encompass the working embodiments is judicially unsound. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the present specification provides sufficient guidance to permit one to

identify those embodiments which are more likely to work than not without actually making and testing them then the present application does not support the breadth of the claims.

In addition, while a specification need not disclose what is well known in the art, that rule does not excuse an applicant from providing a complete disclosure. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Conclusion

Claim 26 is objected to as being dependent upon a rejected base claim.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
OCTOBER 30, 2005